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Effects of ribavirin on hepatitis C-associated nephrotic syndrome in four liver transplant recipients

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Background. Hepatitis C virus infection (HCV) is associated with a variety of extrahepatic disorders such as membranoproliferative glomerulonephritis (MPGN), which is generally due to cryoglobulinemia. After liver transplantation for HCV cirrhosis, alpha-interferon treatment against the recurrence of HCV in the liver graft is poorly effective and may induce intractable graft rejection.

Methods. We describe the cases of four liver transplant recipients treated with ribavirin for HCV-related glomerulopathy and nephrotic syndrome.

Results. The nephrotic syndrome was attenuated or disappeared during ribavirin therapy, and patients showed a marked decrease in proteinuria and an increase in albuminemia. The syndrome relapsed in two patients when ribavirin therapy was stopped, and a favorable response was again obtained in both cases when the treatment was resumed. The main adverse effect of ribavirin was anemia in two patients with renal impairment. No graft rejection occurred.

Conclusions. These findings suggest that continuous therapy with low doses of oral ribavirin may improve the proteinuria of hepatitis C-related glomerulonephritis, at least in liver transplant recipients.

Hepatitis C virus (HCV) infection can be associated with a variety of extrahepatic immunologic disorders. The kidney is one of the major targets of these disorders, the most common complication being membranoproliferative glomerulonephritis, generally due to cryoglobulinemia. Patients with HCV infection and membranoproliferative glomerulonephritis (MPGN) generally have elevated transaminase levels, low complement levels, proteinuria, serum rheumatoid factor and HCV RNA. A positive relationship with a viral load has been suggested, and antiviral treatments such as alpha-interferon have been used with variable results [1, 2]. Other treatments such as plasmapheresis have been attempted, but have potentially severe adverse effects [3, 4].

HCV cirrhosis is one of the most common indications for liver transplantation. After liver transplantation, HCV often recurs in the liver graft and the level of viral replication is much higher than in immunocompetent patients [5]. Due to HCV, the underlying kidney disease and the use of immunosuppressive drugs such as cyclosporine and FK506 can seriously complicate the management of these patients. Furthermore, the use of alpha-interferon, the classical treatment for HCV infection, is difficult in this setting. Indeed, alpha-interferon is poorly efficient and, given its immunostimulating properties, may induce intractable graft rejection in kidney [6] and liver transplant patients [7]. Recently, ribavirin (1-b-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide; Virazole; ICN, Costa Mesa, CA, USA), a nucleoside analog, has been used to treat HCV infection, although it has little or no intrinsic antiviral activity. Its activity seems to be synergistic with that of alpha-interferon in immunocompetent subjects. Its main adverse effect is nonimmune hemolytic anemia, and it does not induce organ rejection.

We describe the cases of four liver transplant recipients with glomerulonephritis due to HCV infection who received ribavirin for the nephrotic syndrome.

METHODS

Patients

Four liver transplant patients with a nephrotic syndrome associated with HCV infection were treated with ribavirin in an open trial of ribavirin involving a total of 24 patients. The other patients had normal renal function. Blood samples were obtained for complete cell counts and routine

Key words: HCV, hepatitis C virus; MPGN, membranoproliferative glomerulonephritis; ribavirin, 1-b-D-Ribofuranosyl-1,2,4-triazole-3-carboxamide; RT-PCR, reverse transcription-polymerase chain reaction.

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Table 1. Biological parameters of the patients before initiation of ribavirin therapy

Patient	Renal Histology	Creatininemia *μM/liter*	Albuminemia *g/liter*	Proteinuria *g/24 hr*	Cryoglobulins *g/liter*	C3	Viremia *copies/ml*
1	MPGN	227	27	4.5	1.2 type II	?	248,000
2	MPGN	138	25	8.0	<0.05	?	750,000
3	MG	165	20	18.0	0.48 type III	normal	660,000
4	MPGN	158	29	1.5	ND type II	↘	20,000

Abbreviations are: MPGN, Membranoproliferative glomerulonephritis; MG, Membranous glomerulonephritis.

biochemical tests. Rheumatoid factor and C3 were quantified by nephelometry (Behring, Marburg, Germany). Serum proteins were separated by zone electrophoresis on agarose (Sebia, Issy-les-Moulineaux, France) and immunofixation electrophoresis was done with the Sebia agarose gel IF kit. Cryoglobulins were isolated from serum stored for seven days (4°C; 0.1 g/liter sodium azide). Cryoglobulin isolation and characterization by immunoblotting was done according to Musset et al [8]. Serum levels were measured as the total protein concentration of each isolated cryoprecipitate by reading absorbance at 280 nm. Serum HCV RNA was quantified with a commercial PCR assay (Amplicor HCV monitor; Roche Diagnostic System, Branchburg, PA, USA) estimating the number of HCV genome copies/ml. Hepatitis B virus (HBV) DNA was quantified with the Digene Hybrid Capture System (Murex Diagnostic Inc., Norcross, GA, USA).

The grade and stage of chronic hepatitis were assessed according to the METAVIR classification [9].

Transjugular renal biopsy was performed. Two-millimeter sections of biopsy tissue were examined after Bouin fixation and paraffin embedding. When frozen tissue was available immunofluorescence studies were performed.

Case reports

Patient 1. Patient 1, a 54-year-old woman, was transplanted for end-stage cirrhosis due to hepatitis B, Delta and C viruses. There was a ten-year history of intractable ascites, hypertension and type II diabetes. She underwent orthotopic liver transplantation in March 1993.

Before transplantation renal function was normal and no proteinuria was detected. Serum cryoglobulin levels were not available but she had no clinical manifestations of cryoglobulinemia.

After transplantation she received a standard immunosuppressive regimen combining azathioprine, methylprednisolone and cyclosporine. Passive immunoprophylaxis with anti-HBs immunoglobulins was given as previously described [10], resulting in HBsAg negativity. Four months after transplantation, serum transaminase levels increased to three times the normal value. A liver biopsy showed mild acute hepatitis with portal and intralobular lymphoid aggregates and features of mild acute rejection. Recurrent HCV disease was diagnosed by the presence of serum HCV RNA. Serum HBsAg, serum HBV DNA and immunohistochemical staining of HBsAg and HBcAg on the liver biopsy specimen were negative.

One year after transplantation, in March 1994, she developed lower limb edema and arterial hypertension. A nephrotic syndrome with proteinuria (4.5 g/24 hr), hypoalbuminemia (27 g/liter) and hyperlipemia was diagnosed. The serum creatinine was 227 μM/liter. A renal biopsy showed MPGN with glomerular thrombi typical of cryoglobulin damage. Mesangial and parietal deposits of IgM(++), IgG(+) and IgA(+) were found on immunofluorescence. High levels (1.2 g/liter) of type II cryoglobulins were detected in the serum and the rheumatoid factor was 11-fold the normal value (110 IU/ml). Characterization of the cryoglobulins showed type II mixed IgG/IgM kappa cryoglobulinemia. Immunofixation of serum revealed a monoclonal peak IgG lambda component (13.1 g/liter). Using the Monitor Amplicor quantitative reverse transcribed-polymerase chain reaction (RT-PCR) test, viremia was quantified at 248,000 copies/ml. HCV-related cryoglobulin glomerulonephritis was diagnosed and antiviral therapy with ribavirin (0.6 g/day then 0.8 to 1 g/day) was started in March 1994. Table 1 summarizes renal function before therapy, and Figure 1A shows the course of biochemical and virologic variables. Ten months after the beginning of antiviral treatment, in January 1995, proteinuria and edema had disappeared and the serum creatinine was 128 μM/liter. By this time albuminemia was in the normal range (40 g/liter) and cryoglobulinemia had fallen to 0.05 g/liter, with a lower titer of rheumatoid factor (19.8 IU/ml); viremia was 115,000 copies/ml and alanine aminotransaminase levels were 1.5-fold normal.

The dose of ribavirin was reduced to 0.6 g/day in May 1995 and the drug was discontinued in September 1995, 18 months after its introduction. Three months later, in December 1995, lower limb edema and arterial hypertension recurred and renal function deteriorated (proteinuria 3.8 g/liter, albuminemia 33.4 g/liter and serum creatinine 130 μM/liter). At this time the serum cryoglobulin level was 0.27 g/liter. Aminotransferase activity was 49 IU/liter and the serum HCV RNA titer was 342,000 copies/ml. Ribavirin therapy was resumed in December 1995, leading, within a month, to a new fall in viremia (47,000 copies/ml), accompanied by lower cryoglobulin levels (0.10 g/liter) and normal renal function (creatinine 100 μM/liter). In April 1996, while still on antiviral treatment, proteinuria was low at 0.2

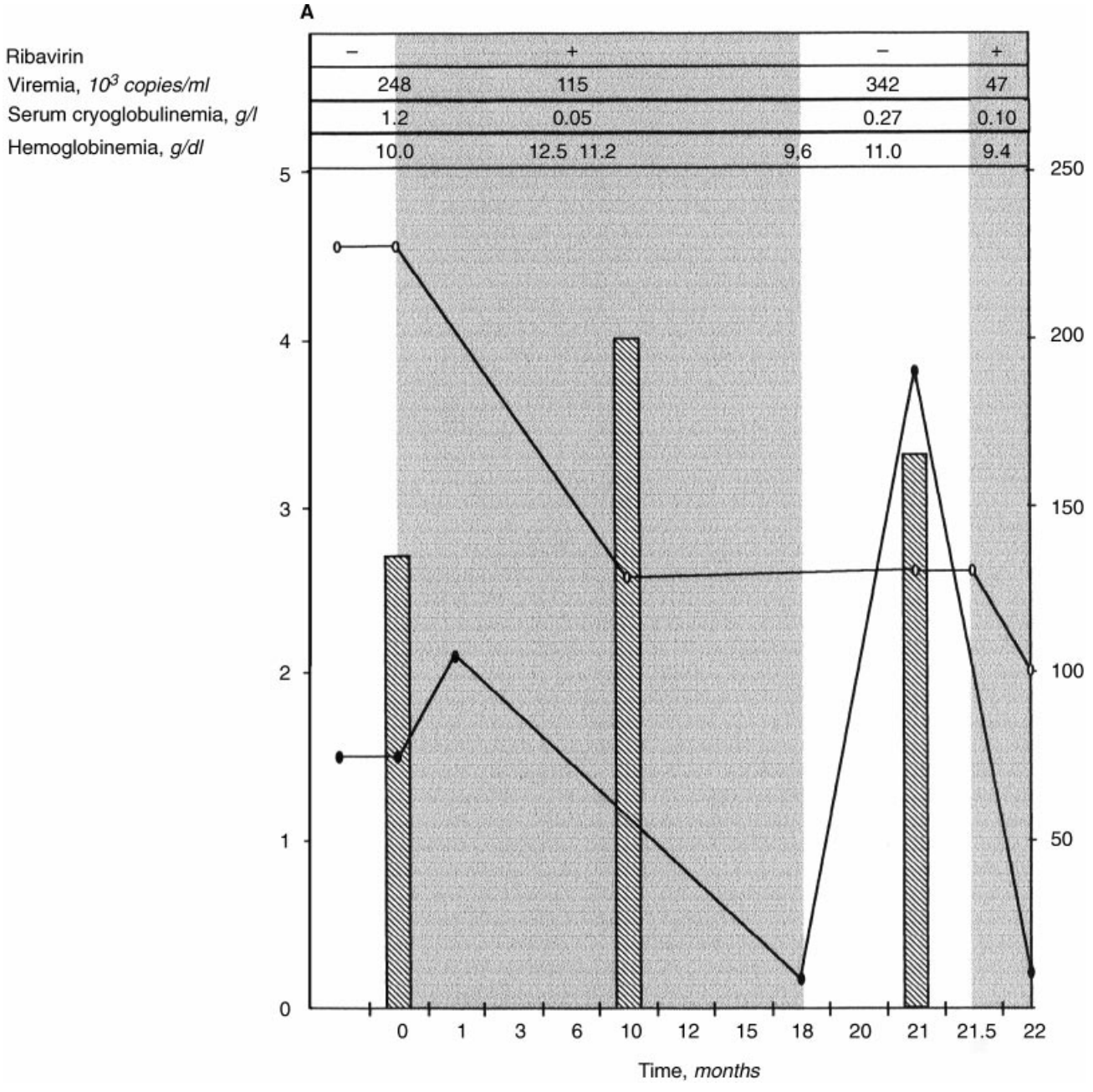


Fig. 1. Laboratory data on patients #1 (*A*), #2 (*B*) #3 (*C*) and #4 (*D*) during ribavirin therapy. Symbols are: (▨) albuminemia, *g/liter*; (●) proteinuria, *g/liter*; (○) creatininemia, *μM/liter*. In (B), (C) and (D), proteinuria is expressed as g/24 hours.

g/liter and aminotransferase levels were normal. At the last visit (December 1997) the patient was well on maintenance ribavirin antiviral treatment, with normal serum creatinine and liver function. A renal biopsy showed unchanged MPGN lesions.

No graft rejection occurred during ribavirin therapy and a moderate anemia was observed.

Patient 2. Patient 2 is a 47-year-old man who underwent orthotopic liver transplantation in October 1996 for HCV-related cirrhosis and hepatocellular carcinoma.

Before transplantation, proteinuria (1 g/24 hr) and mild renal failure were detected (creatinine 120 μM/liter, proteinuria 1 g/24 hr). A renal biopsy showed type I membanoproliferative glomerulonephritis. Immunofluorescence studies showed mesangial staining for IgA (++), IgG (+), IgM (++), C1q (+), C3 (+), kappa light chains (+) and lambda light chains (+). Cryoglobulinemia was mildly positive (0.1 g/liter) and was type II (IgM kappa + IgM lambda + polyclonal IgG). Viremia, assessed using the Amplicor HCV RNA kit, was 20,000 copies/ml.

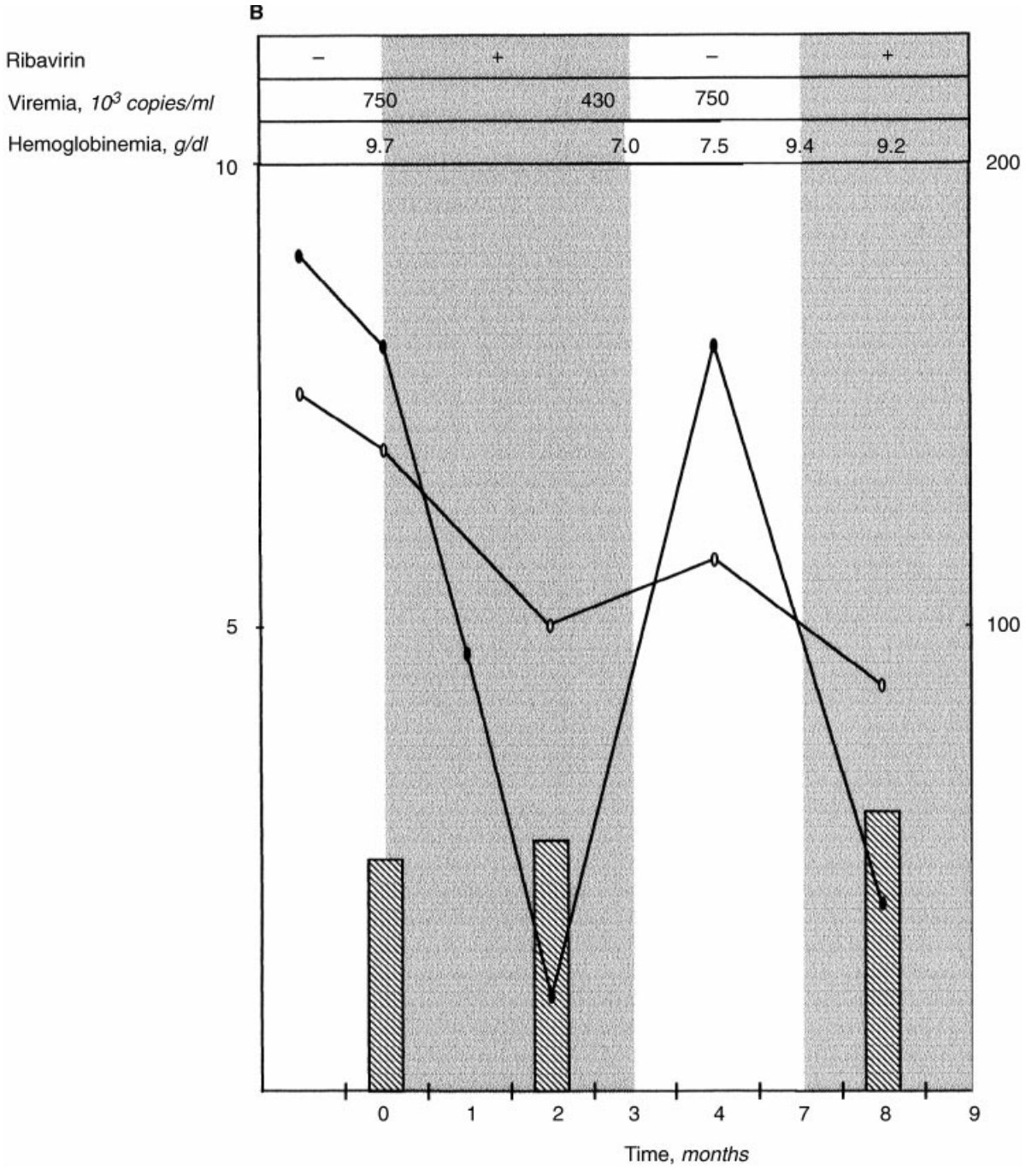
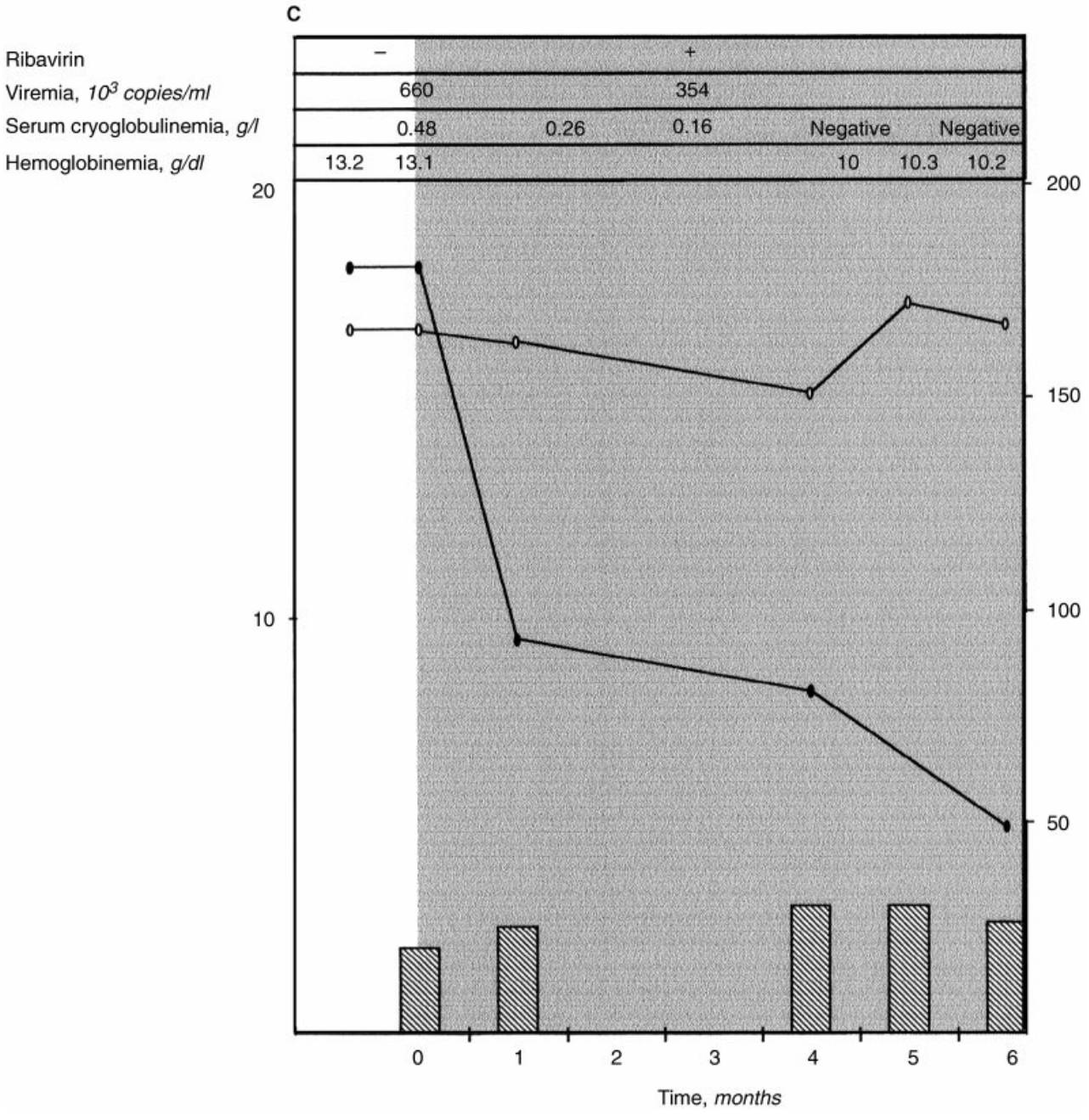


Fig. 1. *Continued.* Symbol key is on page 1313.

After transplantation, despite an initial immunosuppressive regimen excluding cyclosporine and based on the use of antilymphocyte serum, steroids and azathioprine, severe renal failure occurred (creatinine 648 μM/liter, urea 40 mM/liter, proteinuria 10 g/24 hr). The patient was dialyzed for one day. Low-dose cyclosporine was introduced on day 14.

In January 1997, four months after transplantation, a recurrence of hepatitis C was diagnosed by an increase in aminotransferase levels (10-fold normal) associated with high levels of serum HCV RNA (750,000 copies/ml), and was confirmed by liver biopsy showing features of acute lobular hepatitis. The serum creatinine was 138 μM/liter. No cryoglobulins were detected in the serum (<0.05 g/liter). Proteinuria (8 g/24 hr) and hypoalbuminemia (25 g/liter) were observed (Table 1). Mycophenolate (Mefetil; Roche, Neuilly-sur-Seine, France) was introduced to replace azathioprine and maintain effective immunosuppression in spite of the low cyclosporine doses. During the same



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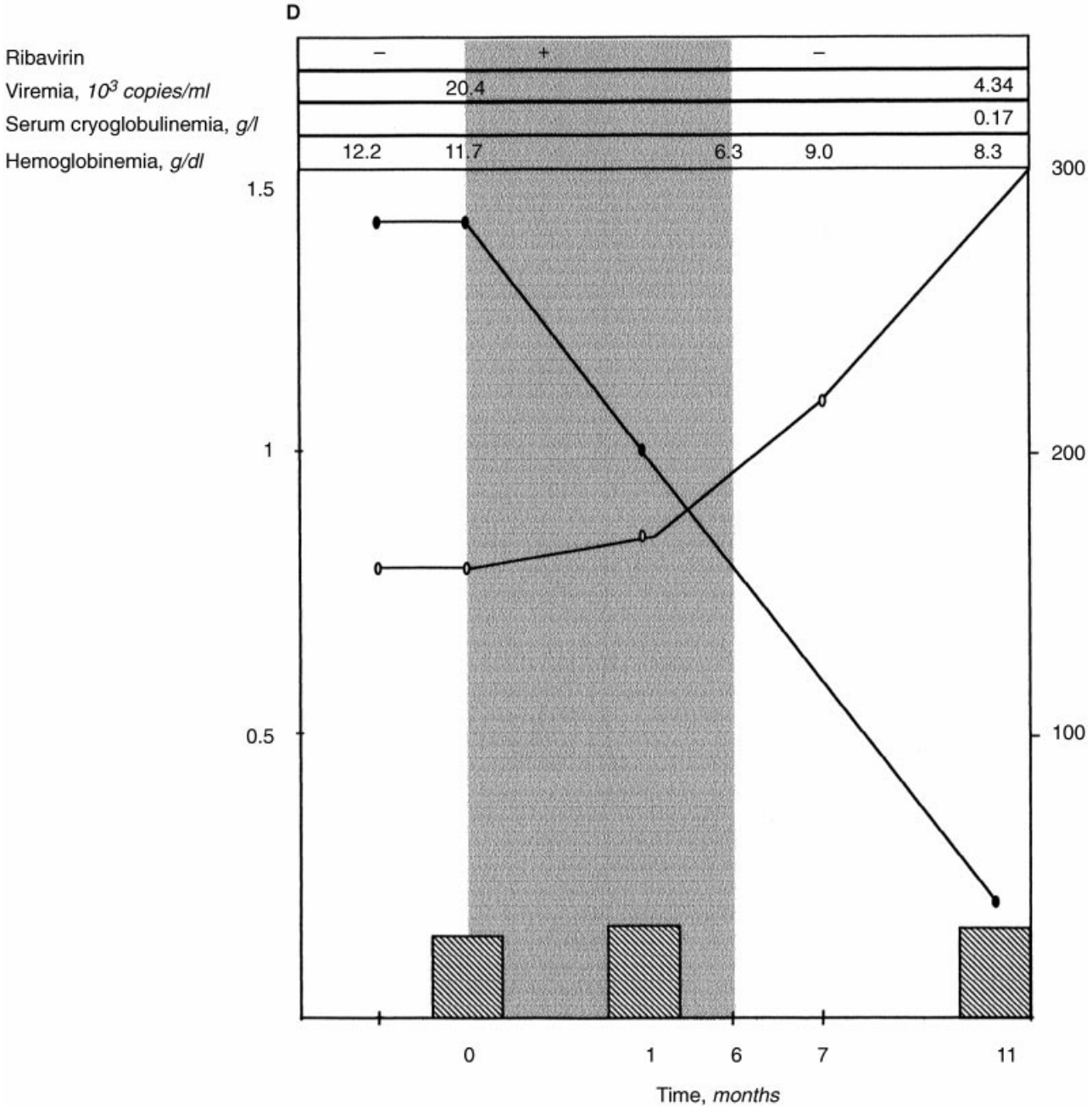
period, ribavirin was started (800 mg/24 hr) and two months later the creatinine was 100 μM/liter, the urea 17 μM/liter, the proteinuria 1 g/24 hours, the albuminemia 27 g/liter and the viremia 430,000 copies/ml; the alanine aminotransferase value was normal (Fig. 1B). At the end of March 1997 the patient was tired and anemic (hemoglobinemia 7 g/dl). No signs of hemolysis were found, and haptoglobin levels and Coomb's test were normal. Erythroblastopenia was confirmed by bone marrow biopsy. Serum parvovirus B19 DNA and antibody to B19 were negative. Ribavirin and mycophenolate were stopped. The nephrotic syndrome reappeared (proteinuria 8 g/24 hr, albuminemia 27 g/liter and serum creatinine 114 μM/liter). HCV viraemia (750,000 copies/ml) was observed in April. In July 1997, central anemia had improved and a low dose of ribavirin (0.4 g/24 hr) was reintroduced to treat the deteriorating nephrotic syndrome. In August 97, the proteinuria was 2 g/24 hours, albuminemia 30 g/liter, and



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creatinine was 87 μM/liter. In September 1997 he was admitted for systemic aspergillosis and died three weeks later from multiple organ failure.

Patient 3. Patient 3, a 47-year-old man, underwent orthotopic liver transplantation in January 1990 for decompensated HCV-related cirrhosis. Renal function was normal and proteinuria was negative before transplantation.

After transplantation, the immunosuppressive regimen consisted of a standard combination of a steroid, cyclosporine and azathioprine; no antiviral therapy was given. In December 1991, two years after transplantation, a recurrence of hepatitis C was diagnosed by a tenfold increase in aminotransferase levels and a liver biopsy showing chronic hepatitis (MetavirA2F1). Alpha-interferon was tried between January and May 1992 but stopped because of signs of chronic rejection (disappearance of biliary tracts in 8 of 12 portal tracts). Alanine aminotransferase activity was sixfold normal. Liver histology, available first in February 1994 then yearly until December 1997, showed both stable lesions of chronic hepatitis (Metavir A2F1) and signs of chronic rejection (disappearance of biliary tracts in 11 of 19 portal spaces on the last biopsy). Lower limb edema and

renal function worsened gradually, with an increase in serum creatinine from 90 μM/liter in 1992 to 121 μM/liter in February 1997, when a nephrotic syndrome was diagnosed. Albuminemia was 23 g/liter and proteinuria 9 g/24 hours. Low levels of cryoglobulins (0.26 g/liter) were found in the serum. Characterization of the cryoglobulins showed type III mixed cryoblobulins. Rheumatoid factor was not found. A renal biopsy showed membranous glomerulopathy with numerous fibrotic glomeruli, capillary wall thickening and subepithelial spikes of glomerular basal membrane. Interstitial tissue was focally fibrous with a degree of inflammation. The cyclosporine dose was reduced to limit renal toxicity. Renal function worsened until August 1997 with serum creatinine 165 μM/liter, albuminemia 20 g/liter, cryoglobulins 0.48 g/liter, and proteinuria 18 g/24 hours. Viremia was 660,000 copies/ml (Table 1).

Antiviral therapy with ribavirin (0.4 g/day) was started in September 1997. In January 1998 the patient felt less tired and lower limb edema was attenuated. Cryoglobulins had disappeared and albuminemia was normal (33 g/liter); his creatinine level was 150 μM/liter and the proteinuria 8 g/24 hours (Fig. 1C). Viremia was 354,000 copies/ml. The ribavirin dose was kept low (0.4 g/day) because of the renal impairment. The last available hemoglobin value was 10 g/dl. In March 1998, renal function remained stable with a fall in proteinuria to 4.8 g/24 hours and a creatinine level of 166 μM/liter.

No graft rejection occurred during ribavirin therapy and a moderate anemia was observed.

Patient 4. Patient 4, a 47-year-old woman, underwent orthotopic liver transplantation in January 1986 for primary biliary cirrhosis. Immunosuppression was based on cyclosporine, steroids and azathioprine. The post-transplant course was marked by the diagnosis of HCV infection in 1993. In April 1994, a liver biopsy showed chronic hepatitis (Metavir A2F3) associated with positive serum HCV RNA.

Before transplantation she had normal renal function which remained so until April 1997, when she developed edema and proteinuria (1.5 g/24 hr). The serum creatinine was 158 μM/liter and the albuminemia 29 g/liter, C3 and C4 were below normal values and the viremia was 20,000 copies/ml; type II mixed IgA/IgM lambda cryoglobulinemia was found. A renal biopsy showed type I membranoproliferative glomerulonephritis (Table 1).

She was treated with ribavirin (0.6 g/24 hr). During the first four weeks of therapy the edema improved and renal function stabilized (serum creatinine 169 μM/liter, albuminemia 33 g/liter and proteinuria 1.0 g/24 hr; Fig. 1D). However, anemia occurred (6.3 g/dl) and a drastic fall in serum haptoglobin levels (0.18 g/liter) was found in September 1997. Ribavirin treatment was stopped, and one month later the anemia had partially recovered (9 g/dl). However, serum creatinine levels were increased to 224 μM/liter and the edema and ascites worsened. In February 1998, viremia was 134,000 copies/ml, proteinuria 0.2 g/24 hours, cryoglobulins 0.17 g/liter, creatinine 306 μM/liter, albuminemia 32 g/liter) and a liver biopsy showed chronic hepatitis (Metavir A1F3). Renal biopsy showed glomerulosclerosis, explaining the low proteinuria. The patient is currently awaiting combined kidney and liver retransplantation.

DISCUSSION

We report our experience of ribavirin therapy in four liver transplant patients with HCV glomerulopathy. Although this was a nonrandomized pilot study, ribavirin appeared to have interesting effects. Indeed, the nephrotic syndrome improved or ceased during ribavirin therapy in all four cases, with a marked fall in proteinuria and an increase in albuminemia. Two patients relapsed when ribavirin was stopped, and a further favorable response was obtained when ribavirin was resumed in both cases.

The nephrotic syndrome is a rare but severe complication of HCV disease. Given its ability to inhibit viral replication, alpha-interferon has also been used in the treatment of extrahepatic complications of HBV and HCV infection. A proportion of patients with HBV infection and MPGN treated with alpha-interferon show an improvement in the nephrotic syndrome [11–15]. As regards patients with HCV infection associated with cryoglobulinemia, a study showed the suppression of viral replication and a decrease in cryoglobulinemia and serum creatinine in 15 of 25 infected patients treated with alpha-interferon [1]. Johnson et al treated 14 patients with HCV-associated MPGN with alpha-interferon for 6 to 12 months [2]. Proteinuria fell by 65%, liver enzymes normalized and viremia decreased, although there was no significant change in serum creatinine. Stehman-Breen et al reported a fall in aminotransferases and viremia in two patients treated with alpha-interferon for HCV-related membranous glomerulonephritis, whereas the nephrotic syndrome worsened in a third patient [16].

After liver transplantation, however, alpha-interferon treatment for recurrent HCV disease is associated with an increased incidence of graft rejection [7], reducing the utility of this drug in the treatment of cryoglobulinemia and its clinical manifestations in this setting. Few cases have been reported in the literature, and most concerned cryoglobulin-associated MPGN. This was also the case of the patients of our study, despite the fact that we did not find cryoglobulins in the serum of patient #2 after transplantation, and that the renal histology of patient #3 showed membranous glomerulonephritis.

Immunosuppressive treatment with steroids, cytotoxic agents (cyclophosphamide or chlorambucil), and/or plasmapheresis have been used in situations where renal impairment is severe. Unfortunately, responses are rare and relapses frequent. Safadi et al reported the case of a patient who developed a nephrotic syndrome after orthotopic liver

transplantation, due to HCV-related cryoglobulins; plasmapheresis without antiviral therapy led to a reduction in the cryoglobulinemia without improving symptoms [11]. In another study Gournay et al reported that plasmapheresis and the addition of cyclophosphamide led to an improvement in the renal disease in one of two cases of MPGN [4]. However, plasmapheresis performed in a patient who developed a nephrotic syndrome following the recurrence of HCV led to a marked reduction in cryoglobulin levels but no improvement in the nephrotic syndrome [3].

Recently, ribavirin has been used to treat chronic HCV infection, and previous studies have shown that oral ribavirin is well tolerated and induces a significant decrease in serum aminotransferases but not in HCV RNA levels [17–19]. However, no information is available on the effect of ribavirin in HCV-related glomerulopathy. In our study the recurrence of HCV infection in three patients and its occurrence in one patient after orthotopic liver transplantation was diagnosed by high levels of HCV RNA in blood and features of hepatitis on liver biopsy, in the absence of HBV recurrence. All the patients had an improvement or cessation of the nephrotic syndrome during ribavirin therapy, with a marked decrease in proteinuria and an increase in albuminemia. Two patients relapsed when ribavirin therapy was stopped, and a favorable response was again obtained when the treatment was resumed in both cases. The most striking finding was that viremia was not significantly changed, despite the apparent effect on both the nephrotic syndrome and aminotransferase activity. We also observed this discrepancy between the biological and virologic responses in the other 20 patients of the open trial including 24 liver transplant patients treated with ribavirin.

Taken together, our findings suggest that ribavirin acts on HCV-related glomerular or liver lesions through a mechanism other than a reduction in viral replication. One possibility is an immunomodulating effect [20, 21]. One of the authors recently showed that a decrease in intrahepatic HCV replication occurs after liver transplantation together with the progression to chronic hepatitis [21]. This suggests that liver injury may be due to immunological phenomena, even after liver transplantation. It is noteworthy that the immunosuppressive regimen was relatively mild in all four patients reported here, either because they were transplanted some time previously, or because of renal failure. It is tempting to speculate that the nonspecific effects of this drug might prove beneficial in nonviral immune glomerulonephritis.

None of the four patients had clinical graft rejection after ribavirin was started. The drug was well tolerated in two patients, whereas anemia occurred in the other two cases. In these latter patients the dose may have been too high, as the half-life of ribavirin elimination is very long and renal impairment considerably favors adverse effects, including anemia. However, the mild global toxicity of ribavirin, as reported in the treatment of chronic hepatitis C [17–19, 22], is compatible with continuous therapy until an alternative emerges. Moreover, long-term use may be limited also by our lack of knowledge on emergence of resistance and/or direct renal effects.

Our findings strongly suggest that ribavirin is effective in treating the clinical and biological manifestations of the nephrotic syndrome due to HCV-related glomerulonephritis, with or without cryoglobulinemia, after liver transplantation. As for the reduction in aminotransferase activity, this was not linked to the ability of ribavirin to reduce viremia, therefore pointing to an immunomodulatory mechanism. As ribavirin does not seem to increase the incidence of rejection (contrary to alpha-interferon), it could be the antiviral drug of choice in this setting.

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